Mayaro Virus Infection, Amazon Basin Region, Peru, 2010–2013
Eric S. Halsey, Crystyan Siles, Carolina Guevara, Stalin Vilcarromero, Erik J. Jhonston, Cesar Ramal, Patricia V. Aguilar, and Julia S. Ampuero

During 2010–2013, we recruited 16 persons with confirmed Mayaro virus infection in the Peruvian Amazon to prospectively follow clinical symptoms and serologic response over a 12-month period. Mayaro virus infection caused long-term arthralgia in more than half, similar to reports of other arthritogenic alphaviruses.

Since the discovery of Mayaro virus (MAYV) in Trinidad in 1954, the etiologic agent of Mayaro fever has been identified in French Guiana, Suriname, Venezuela, Peru, Bolivia, and Brazil (1–9). The presumed primary vectors, Haemagogus mosquitoes, inhabit rural settings and tree canopies, a factor that may explain the relative paucity of cases and restricted endemicity. However, Aedes aegypti mosquitoes have been shown to be competent vectors of MAYV in the laboratory (10), suggesting that an urban-dwelling arthropod could be a vector of this virus on a wider scale. MAYV infection has been demonstrated in tourists returning from the Amazon region, highlighting not only the need to consider MAYV in febrile returned travelers, but also a possible role in global transmission (11).

Incapsulating chronic joint pain has been described with other arthritogenic alphaviruses (12), but little is known about the prognosis and serologic response over long periods after MAYV infection. Therefore, we conducted a prospective 1-year longitudinal study to determine the clinical manifestations and to describe the serologic response among humans with Mayaro fever in the Peruvian Amazon Basin.

The Study

Persons identified for this cohort were recruited in a passive febrile surveillance study in 15 health centers in 4 Peruvian cities: Iquitos, Yurimaguas, Chanchamayo, and Puerto Maldonado (Figure 1). Persons meeting the following criteria were recruited: age ≥5 years, oral/ tympanic temperature ≥38°C (or axillary ≥37.5°C), and no obvious focus of infection. Written consent was obtained from all adults and from a parent or guardian for participants <18 years of age; participants 8–17 years of age also provided written assent. The surveillance period of this study was December 6, 2010–April 30, 2012. Follow-up appointments continued for another year, through April 5, 2013. The institutional review boards of the US Naval Medical Research Unit No. 6 and the Peruvian Ministry of Health approved the protocol.

Compared with the day of the visit for acute illness (acute-phase visit), follow-up evaluations occurred at 20 days (range ±10 days), 3 months (±10 days), 6 months (±15 days), and 12 months (±30 days). At the acute-phase visit and at all follow-up visits, a blood sample was obtained.

For every participant, we attempted to determine the cause of infection by testing acute-phase serum for virus in Ae. albopictus (C6/36) and African green monkey kidney (Vero 76) cell culture (with immunofluorescence assay) and for viral nucleic acid by reverse transcription PCR (RT-PCR). Capture IgM and IgG ELISAs were performed at 1:100 dilution on the acute-phase and all follow-up samples to evaluate antibody responses to MAYV and other endemic arboviruses (i.e., Venezuelan equine encephalitis, Oropouche, group C, Guaroa, and dengue viruses) (6). Samples with detectable IgM or IgG were serially diluted and retested. Seroconversion was defined as a ≥4-fold increase in IgM titer between the acute-phase visit and the second visit. A Mayaro fever case was defined as IgM seroconversion or virus detected by isolation or by RT-PCR. In addition, we collected throat swabs from participants with pharyngeal erythema at the acute-phase visit and urine samples from the 3-month follow-up visit to determine the presence of MAYV with RT-PCR (13).

Of 2,094 febrile participants enrolled, 16 (0.8%) had Mayaro fever (Table 1). Of the 16 persons with Mayaro fever, 11 had MAYV isolated by the cell culture assays (11 in both Vero 76 and C6/36), 13 were MAYV positive by RT-PCR, and all had IgM ELISA seroconversion between the acute-phase and 20-day follow-up visits (Table 1). In all 16 participants, no IgM ELISA seroconversion occurred for endemic non-alphavirus viruses (i.e., Oropouche, group C, Guaroa, and dengue viruses). Four participants demonstrated IgM ELISA seroconversion against another alphavirus, Venezuelan equine encephalitis virus, but these 4 all had MAYV identified by immunofluorescence assay and by RT-PCR. Using RT-PCR, we did not detect MAYV in 2 acute visit throat swabs, any second-visit (20-day) serum samples, and any third-visit (3-month) urine samples.
Besides fever, the most common symptoms affecting participants in the acute stage of MAYV infection were malaise, headache, arthralgia, myalgia, and retro-orbital pain. The prevalence of these and other nonjoint signs and symptoms at the acute-phase and follow-up visits are available in the online Technical Appendix Table, wwwnc.cdc.gov/EID/articledpdfs/19/11/13-0777-Techapp1.pdf.

Although reports of joint pain waned in study participants by the second (20-day) visit, complaints increased at 3 months and persisted in 54% even after 12 months. Joints of the hand, wrist, elbow, feet, and knee were identified as problematic, whereas hip or axial joint pain was rare (Figure 2). The chronic joint pain often interfered with activities of daily living (Table 2).

Table 1. Demographic factors and laboratory findings at 5 encounters for patients with MAYV infection, Amazon Basin region, Peru, 2010–2013*  

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, y/sex</th>
<th>Day of illness at enrollment</th>
<th>Isolation</th>
<th>RT-PCR†</th>
<th>Acute phase</th>
<th>Day 20</th>
<th>Month 3</th>
<th>Month 6</th>
<th>Month 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12/F</td>
<td>2</td>
<td>MAYV</td>
<td>MAYV</td>
<td>0; 0</td>
<td>6,400; 100</td>
<td>0; 6,400</td>
<td>0; 25,600</td>
<td>0; 25,600</td>
</tr>
<tr>
<td>2</td>
<td>28/F</td>
<td>2</td>
<td>MAYV</td>
<td>MAYV</td>
<td>0; 0</td>
<td>1,600; 100</td>
<td>0; 1,600</td>
<td>0; 6,400</td>
<td>0; 25,600</td>
</tr>
<tr>
<td>3</td>
<td>19/F</td>
<td>4</td>
<td>Neg</td>
<td>Neg</td>
<td>0; 0</td>
<td>6,400; 100</td>
<td>0; 1,600</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>11/M</td>
<td>2</td>
<td>MAYV</td>
<td>MAYV</td>
<td>0; 0</td>
<td>1,600; 100</td>
<td>0; 1,600</td>
<td>0; 1,600</td>
<td>0; 6,400</td>
</tr>
<tr>
<td>5</td>
<td>41/F</td>
<td>2</td>
<td>MAYV</td>
<td>MAYV</td>
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<td>25,600; 400</td>
<td>0; 1,600</td>
<td>0; 1,600</td>
<td>0; 6,400</td>
</tr>
<tr>
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<td>Neg</td>
<td>0; 0</td>
<td>6,400; 1,600</td>
<td>0; 1,600</td>
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<td>–</td>
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<tr>
<td>7</td>
<td>36/F</td>
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<td>MAYV</td>
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<td>6,400; 100</td>
<td>0; 102,400</td>
<td>0; 409,600</td>
<td>0; 102,400</td>
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<tr>
<td>8</td>
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<td>0; 25,600</td>
<td>0; 25,600</td>
</tr>
<tr>
<td>9</td>
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<td>0; 6,400</td>
<td>0; 6,400</td>
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<tr>
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<td>0; 1,600</td>
<td>0; 6,400</td>
<td>0; 25,600</td>
</tr>
<tr>
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<td>46/F</td>
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<td>12</td>
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<td>1,600; 400</td>
<td>0; 25,600</td>
<td>0; 25,600</td>
<td>0; 25,600</td>
</tr>
<tr>
<td>14</td>
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<td>MAYV</td>
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<td>1,600; 400</td>
<td>0; 25,600</td>
<td>0; 6,400</td>
<td>0; 6,400</td>
</tr>
<tr>
<td>15</td>
<td>11/M</td>
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<td>MAYV</td>
<td>MAYV</td>
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<td>1,600; 400</td>
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<td>0; 25,600</td>
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<tr>
<td>16</td>
<td>64/M</td>
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<td>Neg</td>
<td>MAYV</td>
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<td>6,400; 25,600</td>
<td>400; 6,400</td>
<td>0; 6,400</td>
<td>0; 6,400</td>
</tr>
</tbody>
</table>

*LEG, Leg; RT-PCR, reverse transcription polymerase chain reaction; Neg, negative; –, visits not attended by the patient.
†Isolation and RT-PCR results are from the acute-phase visit.
‡For ELISA IgM and IgG results, endpoint titration values were determined. All serology values are expressed as inverse titers.
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symptoms in the fingers. Involvement of joints of the wrist,
to 12 months, most of these studies identified persistent
sons. By using follow-up periods ranging from 1 month
were either solitary case reports or case series of <4 per-
2, 5–9), although all of these
– 9, after MAYV infection (11).
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nostic data to share with patients. It also indicates the need
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Previous reports have documented persistent joint pain
Mayaro fever after day 3 of symptoms, suggesting
culture were negative in the only 2 participants in our study
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participants identified by serology, both RT-PCR and cul-
ture were more sensitive than what others have found for
Sindbis virus infection, for which 1 study found sensitivities
7% and 1%, respectively (15). However, RT-PCR and cul-
ture were negative in the only 2 participants in our study
who had Mayaro fever after day 3 of symptoms, suggesting
a narrow window when these assays may be effective.
No effective vaccine or antiviral agent exists for the
arthritogenic alphaviruses, and treatment relies mainly on
supportive modalities, such as nonsteroidal anti-inflam-
matory medications (12). Our results offer evidence that
MAYV, similar to other alphaviruses, may cause protracted
joint symptoms and provide further impetus to the develop-
ment of more effective preventive and treatment strategies.

Conclusions
This study demonstrated that persons with acute Maya-
ro fever often have many nonspecific symptoms but may
continue to have chronic joint pain for at least 1 year after
acute illness. Our study offers physicians valuable prog-
nostic data to share with patients. It also indicates the need
to consider MAYV infection in patients with seronegative
arthritis (i.e., negative rheumatoid factor and antinuclear
antibodies) in regions to which MAYV is endemic.

Previous reports have documented persistent joint pain
after MAYV infection (2–5,9,11), although all of these
were either solitary case reports or case series of ≤4 per-
sons. By using follow-up periods ranging from 1 month
to 12 months, most of these studies identified persistent
symptoms in the fingers. Involvement of joints of the wrist,
ankle, and knee also were mentioned, similar to the partici-
pants in our study.

Long-term manifestations of infection with other al-
phaviruses have been more robustly characterized, with
persistent arthralgia being commonly described. Follow-
up of chikungunya virus–infected patients on Réunion
Island revealed that >60% had joint pain >3 years after
acute illness that most often affected the fingers, wrists,
knees, and ankles (14). Sindbis virus infection in a co-
hort in Finland resulted in persistent arthralgia lasting at
least a year in half of those infected, with ankles, fingers,
and wrists being most often affected (15). One caveat of
our study and other studies is the difficulty in definitively
attributing persistent arthralgia solely to viral infection,
although our participants’ limitations in activities of
daily living were all described as starting after their acute
Mayaro fever illness.

IgM seroconversion occurred in all of the participants
in our study that were identified with either isolation or RT-
PCR, consistent with another report that noted the reliability
of serology in detecting MAYV infection (9). In our study
participants identified by serology, both RT-PCR and cul-
ture were more sensitive than what others have found for
Sindbis virus infection, for which 1 study found sensitivities
of 7% and 1%, respectively (15). However, RT-PCR and cul-
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The authors have declared that no competing interests exist. The corresponding author had full access to all data in the study and final responsibility for the decision to submit this publication.

Dr Halsey is a board-certified infectious diseases physician, US Air Force officer, and Virology Department head at the US Naval Medical Research Unit No. 6 in Lima, Peru. His research interests include the clinical and epidemiologic aspects of flavivirus, alphavirus, and bunyavirus infections.

References


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Technical Appendix

Technical Appendix Table. Signs and symptoms in 16 patients with Mayaro virus infection at the acute-phase and each follow-up visit, Amazon Basin region, Peru, 2010–2013.

<table>
<thead>
<tr>
<th>Sign or symptom</th>
<th>Acute-phase visit</th>
<th>Day 20</th>
<th>Month 3</th>
<th>Month 6</th>
<th>Month 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malaise</td>
<td>16/16</td>
<td>2/16</td>
<td>4/16</td>
<td>1/14</td>
<td>2/13</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>15/16</td>
<td>3/16</td>
<td>11/16</td>
<td>8/14</td>
<td>7/13</td>
</tr>
<tr>
<td>Headache</td>
<td>15/16</td>
<td>2/16</td>
<td>6/16</td>
<td>4/14</td>
<td>4/13</td>
</tr>
<tr>
<td>Myalgia</td>
<td>14/16</td>
<td>1/16</td>
<td>1/16</td>
<td>2/14</td>
<td>2/13</td>
</tr>
<tr>
<td>Pain behind eyes</td>
<td>12/16</td>
<td>0/16</td>
<td>1/16</td>
<td>1/14</td>
<td>0/13</td>
</tr>
<tr>
<td>Anorexia</td>
<td>12/16</td>
<td>0/15</td>
<td>1/16</td>
<td>0/14</td>
<td>1/13</td>
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<td>0/15</td>
<td>1/16</td>
<td>0/14</td>
<td>0/13</td>
</tr>
<tr>
<td>Vomiting</td>
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<td>0/15</td>
<td>1/16</td>
<td>0/14</td>
<td>0/13</td>
</tr>
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<td>Dizziness</td>
<td>10/16</td>
<td>1/16</td>
<td>1/16</td>
<td>1/14</td>
<td>2/13</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>10/16</td>
<td>0/15</td>
<td>0/16</td>
<td>0/14</td>
<td>1/13</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>8/16</td>
<td>1/15</td>
<td>1/16</td>
<td>0/14</td>
<td>0/13</td>
</tr>
<tr>
<td>Rash</td>
<td>8/16</td>
<td>0/15</td>
<td>0/16</td>
<td>0/14</td>
<td>0/13</td>
</tr>
<tr>
<td>Sore throat</td>
<td>4/16</td>
<td>0/16</td>
<td>1/16</td>
<td>1/14</td>
<td>0/13</td>
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<tr>
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<td>4/15</td>
<td>0/16</td>
<td>1/16</td>
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